DETAILED ACTION

Applicant's response without traverse, received 2/8/08, in response to the restriction/election requirements, mailed 8/9/07, electing invention I (which includes claims 1-46 and 67), drawn to a method of treating a hyperproliferative disorder in a mammal comprising simultaneously or sequentially administering a composition species (see specification, pages 37-38, Example 6) comprising doxorubicin as the antineoplastic agent species and : (i) a therapeutically effective amount of certain antineoplastic agents, and (ii) a therapeutically effective amount of a compound of formula 1 i.e. Compound X (the mesylate salt of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-(3-4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide as the compound (formula 1) species, is acknowledged.

Applicant's claim amendment filed 2/8/08 is also acknowledged.

Status of the Claims

Claims 1-41, 43-47, and 67 are currently pending in this application.

Claims 2-10, 13-17, 21, 23-25, 34, 39-41, 44-47 are withdrawn for being directed non-elected subject matter.

Claims 1, 11, 12, 18-20, 22, 26-33, 35-38, 43, and 67 are presented for examination.

Restriction/Election

The restriction/election requirements are made final.

Objection to the Specification

The use of the trademark "Camptosar" has been noted in this application (e.g. page 2). All trademarks should be capitalized wherever they appear in the specification and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Thus, applicant may correct the above noted deficiency by simply replacing the brand name(s) with the generic name.

It is noted that applicant is required to review the specification for any inappropriate use of trademarks and correct any deficiencies as suggested above.

Objection to the Claims

Claims 1 and 67 are objected to for use of improper Markush claim language (see MPEP 2173.05(h).

Claims 1 and 67 recite "a therapeutically effective amount of a taxane derivative, a platinum coordination complex selected from the group consisting of carboplatin, tetraplatin, and topotecan, a nucleoside analog selected from the group consisting of gemcitabine hydrochloride and 5-FU, an anthracycline, a topoisomerase selected from the group consisting of etopside, teniposide, amsacrine, topotecan, and Camptosar®, an aromatase inhibitor," which does not comply with proper Markush claim language.

Claims 1 and 67 are objected to for reciting the trademark "Camptosar." It should be capitalized wherever it appears and also be accompanied by the generic

terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Thus, applicant may correct the above noted deficiency by simply replacing the brand name with the generic name.

Claim 1 is also objected to for using improper punctuation by reciting the term "5_FU." It is suggested that this objection may be overcome by deleting said term and replacing it with the full generic name followed by the term "5-FU" in parenthesis.

Claim 32 is objected to for having extraneous markings at the right margin of the claim.

Applicant is required to correct the above deficiencies.

Claim Rejections – 35 USC 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 11, 12, 18-20, 22, 26-33, 35-38, 43, and 67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for methods of treating certain hyperproliferative diseases, including breast cancer, with certain combinations of drugs, does not reasonably provide enablement for methods of treating any and alll hyperproliferative diseases with any and all combinations of drugs encompassed by the claims. This is a scope of enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if its is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth in *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman* 230 USPQ 546 (BdApls 1986) at 547 the court cited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art.

The invention in general relates to a method of treating a hyperproliferative disorder in a mammal comprising a combination of a certain chemotherapeutic agent and a compound of formula I or prodrug thereof.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. It is noted that the chemical and medical arts are generally unpredictable, requiring each embodiment to be individually assessed for chemical, pharmacologic, pharmaceutical, and clinical efficacy. The more unpredictable an area, the more specific enablement is necessary in order to satisfy the statue. (see *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970)).

Burrell et al (US Patent 6,692,773) teach in spite of many years of research on the treatment of hyperproliferative skin disorders and diseases such as psoriasis, there are still many patients suffering from such skin diseases for whom treatment regimes have been ineffective and that many of the side effects from the medications currently prescribed for the treatment of psoriasis are problematic (col. 1). Burrell et al. teach that there still remains a need for a safe and effective treatment for

hyperproliferative skin disorders and diseases such as psoriasis and keratinization (col. 1, lines 19-27).

2. The breadth of the claims

The instant claims are relatively broad in scope. Claim 1 encompasses a multiplicity hyperproliferative diseases, including cancerous and non-cancerous conditions. Claim 24, for example, recites the term "non cancerous" which is very broad. Claim 25 recites the term "benign hyperplasia of the skin" which is also very broad. Also, claim 1 encompasses a multiplicity of different combinations of drugs, which would reasonably exhibit different/varying therapeutic and adverse effects, depending the specific combination of actives. Also, claim 1, for example, encompass prodrugs of compounds formula I, and taxane derivatives, which are not disclosed in the specification in a way for someone of skill in the art to reasonably ascertain the chemical structures of said prodrugs. Thus, one of ordinary skill in the art would need to conduct undue experimentation to establish the chemical structure as well as determine the therapeutic activity of said prodrugs and taxane derivatives encompassed by the instant invention.

3. The amount of direction or guidance provided and the presence or absence of working examples

Based on the instant disclosure, the applicant at best has provided specific direction or guidance only for a general method of treating hyperproliferative disorders. No reasonably specific guidance is provided concerning useful therapeutic protocols (e.g. dosages) or specific agents for treating benign hyperplasia of the skin, for

example, comprising doxorubicin, which is a known to cause serious skin damage upon contact with skin tissue, is disclosed.

4. The quantity of experimentation necessary

In view of the uncertainty and unpredictability of the art as evidenced by the discussion of the prior art, it is reasonable to surmise that this level of uncertainty in the art would require one skilled in the art to conduct more than routine experimentation in order to practice the claimed invention commensurate with the scope of the claims.

For the reasons stated above, claims 1, 11, 12, 18-20, 22, 26-33, 35-38, 43, and 67 are rejected under 35 USC 112, first paragraph, for lack of scope enablement because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims.

Claim rejections – 35 USC 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 USC 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 11, 12, 18-20, 22, 26-33, 35-38, 43 and 67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 67 recite the term “Camptosar,” but fails to state the full meaning of the term at the first occurrence in the claim set. This limitation is vague and indefinite because it is not clear what this term specifically mean. It is suggested that this specific rejection may be overcome by either replacing the terms with their full generic name or,

alternatively, amend the claim by inserting the full name in parenthesis at the first occurrence of the term in the claim set. It is also noted that even though the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Dependent claims 11, 12, 18-20, 22, 26-33, 35-38, and 43 are rejected for the same reason as these claims fail to correct the deficiency of the claim from which they depend.

In addition, claims 1 and 67 recite the confusing language “a therapeutically effective amount of a taxane derivative, a platinum coordination complex selected from the group consisting of carboplatin, tetraplatin, and topotecan, a nucleoside analog selected from the group consisting of gemcitabine hydrochloride and 5-FU, an anthracycline, a topoisomerase selected from the group consisting of etopside, teniposide, amsacrine, topotecan, and Camptosar®, an aromatase inhibitor,” which renders the claim indefinite because it is not clear what members constitute the Markush group or groups recited therein. The recitation of the term “an aromatase inhibitor" makes said term even more confusing. For these reasons, claims 1 and 67, and dependent claims 11, 12, 18-20, 22, 26-33, 35-38, and 43 are found to be indefinite.

Claim 12 recites “[t]he method according to claim 10, wherein the anthracycline is doxorubicin,” which renders the claimed subject indefinite as claim 10 fails to provide a

proper antecedent basis for the term “the anthracycline” since it is directed towards a nucleoside analog (i.e. 5-FU).

LACK OF WRITTEN DESCRIPTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

Claims 1, 11, 12, 18-20, 22, 26-33, 35-38, 43 and 67 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses chemicals which meet the written description and enablement provisions of 35 USC 112, first paragraph. However, claims 1, 11, 12, 18-20, 22, 26-33, 35-38, 43 and 67 are directed to encompass undisclosed anthracyclines, and/or taxane derivatives, and/or prodrugs or solvate thereof of formula 1 as recited in claim 1(see claims 1, 38, and 67) which only correspond in some undefined way to specifically instantly disclosed chemicals. None of the undisclosed compounds meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the above specifically disclosed chemical structures, the

skilled artisan cannot envision the detailed chemical structure of the encompassed compounds, analogs, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only the disclosed chemically structurally defined chemicals, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See page 1115.)

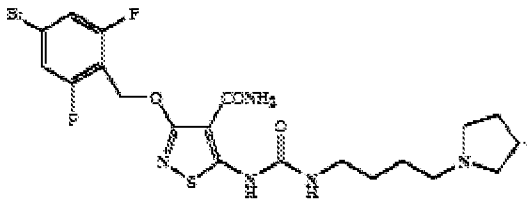
Claim rejections – 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 11, 12, 18-20, 22, 26-33, 35-38, 43, and 67 are rejected under 102(e) as being anticipated by Gant et al. (US Patent 6,831,091).

Gant et al. teach a method of treating hyperproliferative disorder in a mammal comprising administering to the mammal a therapeutically effective amount of the below compound, including the mesylate salt form i.e. applicant's elected compound species of formula I as recited in instant claim 1, and a pharmaceutically acceptable carrier, wherein the hyperproliferative disorder is a cancer such as breast cancer (see abstract and col. 10, line 59 to col. 11, line 11):



Instant claims 19, 20, and 21 recite the term breast cancer. Claim 22 recites the term "metastatic breast cancer" which is construed to overlap with the term "breast cancer." Gant et al. teach that the active compound may be applied as a sole therapy or may involve one or more other anti-tumor substances, for example, mitotic inhibitors,

alkylating agents, antimetabolites, cell cycle inhibitors, intercalating antibiotics (e.g. adriamycin (i.e. doxorubicin). See col. 16, lines 35-54. Claims 11 and 12 recite the term “doxorubicin; instant claims 1 and 67, for example, recites the term "(i) a therapeutically effective amount of …, an anthracycline, … and (ii) a therapeutically effecitce amount of a compound of formula 1,” which overlaps with the teaching of Gant et al. (see col. 16, lines 35-54). Gant et al. teach that the conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment (col. 16, lines 51-54). Claims 1 and 67, for example, recite the term "either simultaenously or sequentially; " claim 26 recites the term “wherein said compounds ... are administered simultaneously;” and claim 27 recites the term “wherein said compounds ... are administered sequentially;” said terms overlaps with the teaching of Gant et al. (col. 16, lines 51-54). Gant et al.

For the above reasons, claims 1, 11, 12, 18-20, 22, 26-33, 35-38, 43, and 67 are found to be anticipated by the cited reference (see also reference claims 29-31).

Claim rejections – 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 11, 12, 18-20, 22, 26-33, 35-38, 43, and 67 are rejected under 102(e)

as being anticipated by Larson et al. (US Patent 6,235,764).

The above discussion of Grant et al. is incorporated by reference as said teachings are essentially identical to the teachings of Larson et al.

Larson et al. teach applicant's elected compound of formula I (col. 4, line 66 to col. 5, line 3). Larson et al. teach a method of treating hyperproliferative disorders, including cancers such as breast cancer (col. 6, line 56 to col. 7, line 2; and col. 7, lines 31-63). Larson et al. teach method for treating a mammal with a hyperproliferative disorder comprising administering to said mammal a therapeutically effective amount of a compound of the below formula, or a pharmaceutically acceptable salt or hydrate thereof, in combination with an anti-tumor agent selected from the group consisting of …, intercalating antibiotics …" such as adriamycin (i.e. doxorubicin). See col. 7, lines 31-63; and col. 24, line 52 to col. 25, line 40. Larson et al. also teach that said combination therapy may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment (col. 25, lines 1-4).

For the above reasons, claims 1, 11, 12, 18-20, 22, 26-33, 35-38, 43, and 67 are found to be anticipated by the cited reference.

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Alternatively, claims 1, 11, 12, 18-20, 22, 26-33, 35-38, 43, and 67 are rejected under 103(a) as being unpatentable over Gant et al. (US Patent 6,831,091) or Larson et al. (US Patent 6,235,764).

The above discussions of Gant et al. and Larson et al. are incorporated by reference.

Based on the teaching of Gant et al. or Larson et al., someone of skill in the art would have been motivated to create the instant claimed inventive concept.

Thus, someone of skill in the art at the time the instant invention was made would have found it obvious to create the instant claimed invention with reasonable predictability.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http:pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 800-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

9 April 2008

Examiner /C.R./

/Brian-Yong S Kwon/

Primary Examiner, Art Unit 1614